## REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

The first paragraph of the application has been corrected, and the paragraph bridging pages 14 and 15 has been amended, as has the paragraph bridging pages 100 and 101. Claims 1, 18, and 48 have been amended, and claims 54-63 have been added. Claims 1, 18, 28, 32-34, 48-51 and 54-60 are in the case and are before the Examiner.

### A. The Amendments

The specification has been amended at page 1, in the first paragraph to correct the history of the application. The specification has also been amended at page 14 pursuant to the Examiner's helpful suggestion. The status of the published PCT application as a US Patent (No. 6,630,161) has been up-dated at pages 100-101 and the inadvertent recitation of the emulsion of that patent being a water-in-oil emulsion has been corrected to be an oil-in-water emulsion as can be seen from the abstract of that patent, a copy of which is attached for the Examiner's convenience as Exhibit A.

Each of the independent claims (1, 18 and 48) has been amended to recite that the immunogenic particles are dispersed in a pharmaceutically acceptable diluent emulsion that includes an adjuvant. Support for those amendments can be found at least at pages 96-101. Those claims have also been amended to recite a preferred amount of substitution and the sequences against which the substitutions are compared. Specific support for that amendment can be found in the specification at page 70 through page 72. Each independent claim has further been amended to clarify that the sequence or residue inserted into the HBc immunogenic loop renders the immunogenic particles less antigenic than are native HBc particles. Specific support for this amendment can be found at least at page 42, second full paragraph.

Claim 18 has also been amended to recite that the HBc sequence portion of the chimer begins at least at residue 4, rather than residue 5. This amendment is supported at least by the disclosures of original claims 1 and 48, as well as the disclosures at least at pages 18, 33, 41 and page 60.

New claims 54-60 recite that the adjuvant includes aminoalkyl glucosamine phosphate and squalene. Support for those claims can be found at least in the disclosures at pages 96-101. New claims 61-63 are directed to the use of a preferred chimer molecule from which the immunogenic particles are prepared that has the Cys residues at HBc positions 48 and 107 replaced by other residues, while the other native internal Cys residue at position 61 is present. Specific support for these claims can be found at least at pages 72-73.

As requested in the Action, clearer copies of Figs. 8-10 are enclosed herewith.

It is thus seen that no new matter has been added.

### B. Rejections Under 35 USC §112

#### 1. Second Paragraph

##### a. First Rejection

The pending claims have been rejected under the Second Paragraph of Section 112 as allegedly being indefinite. The basis for the rejection is understood to be that the claims recite that there can be one to three cysteines at a position -20 to +1 of the HBc sequence and to conform to that definition, additional residues must be present. The Action asked whether the presence of additional residues at positions 2 and 3 was intended and the answer is that they can be, but need not be present. Put differently, the claims are open to that possibility, but do not require it, nor do they prohibit that inclusion.

The Examiner's attention on this point is invited to the two full paragraphs on page 38 of the present specification. The meaning of the phrase "-20 to about +1 from the N-terminus of SEQ ID NO:1" is explained, as is a method of determining such a position. The second of those paragraphs states in part:

> [i]nasmuch as amino acid residue sequences are normally shown from left to right and in the direction from N-terminus to C-terminus, any aligned chimer molecule residue to the left of the position that can be occupied by the HBc start methionine has a negative position. A contemplated cysteine residue can occur at a position about twenty residues to the left of the aligned start methionine of HBc to the position corresponding to that start methionine. (Emphasis supplied.)

Thus, all one needs to do is align the questioned sequence with that of SEQ ID NO:1 to determine a position in the negative sequence region. There is no mention of a requirement that the HBc residues of positions 2 and 3 be present, as a consequence, those residues can be present, but need not be so. The Examiner's attention is further invited to Table 9 at page 132 of the specification for illustrations of chimeric molecules wherein a cysteine-containing sequence is bonded to residue 4 of the HBc sequence as the first HBc residue. It is thus submitted that there is no indefiniteness as the claims recite exactly what is intended, and that this rejection should be withdrawn.

### b. Second Rejection

All of the claims were also rejected as allegedly indefinite because of an alleged lack of clarity in the step of "maintaining said patient". The Action asked whether the treatment were to be "maintained until the T-cell immune response is induced" or whether "the patient is maintained under supervision until such time that the T-cell response is activated and confirmed". Of the two positions, the second is the one intended as maintaining treatment would imply that a continuous immunization is implied. Rather, as noted at least at page 74 the patient is maintained for about 3 to about 12 weeks and can be given a booster injection or further immunization. It is thus believed that the claim is not indefinite and that the basis for rejection is moot or otherwise overcome.

## 2. First Paragraph

### a. Written Description

All of the pending claims were rejected as allegedly failing to comply with the written description requirement in that the claims were said to contain subject matter not described in the specification so as to reasonably convey to a skilled worker that the inventors were in possession of the invention at the time the application was filed. More specifically, the Action indicated that the recitation of variations of up to about 10% or 20% from the native HBc sequence causes several grounds of uncertainty as to whether the claimed subject matter would function as a T cell stimulator.

Although it is believed that this basis for rejection is inappropriate as it is couched in terms of enablement rather than description and the relied on Bowie and Riffkin articles do not deal with T cell stimulation by HBc peptides or proteins. Further, reliance on the Sarobe teaching regarding modifications in HCV deals with hepatitis C rather than hepatitis B virus and is likewise inapt.

The Examiner's attention is invited to the teachings of US Patents No. 4,882,145 and No. 4,818,527, both to Thornton et al., that are disclosed on page 9 of the specification and noted in the IDS as documents A4 and A5, respectively. Those patents illustrate the T cell stimulatory power of eleven peptides taken from the HBc sequence. It is respectfully submitted that the skilled worker to whom this invention is directed would know of the presence and location of at least those T cell-stimulating epitopes and would not destroy them in preparing a HBc chimer about 10% to about 20% conservative substitutions. This basis for rejection should therefore be withdrawn.

Although it cannot be agreed that the claims were not within the written description, the claims have been amended to further limit the percentage of possible substitutions. It is thus submitted that the rejection is moot.

The Examiner's attention is also invited to the disclosures of US Patent No. 6,964,769 to Sebbel et al., that just came to counsel's attention as discussed hereinafter. Claim 1 and all of the dependent claims of that presumptively valid patent recite a named polypeptide sequence "or a sequence having at least 90% sequence identity to said polypeptide sequence . . ."

Counsel was unable to find any disclosure as to the identity of the up to 10% substituting residues, as compared to the lower percentage of substitutions in the amended claims herein. It is thus submitted that the present claims define a more limited number of chimers than those of the presumptively valid issued patent that claims similar, but different chimers. It is therefore submitted that the applicants were in possession of a very large number of the desired chimer molecules as of the filing date, and that this portion of the rejection should be withdrawn.

## b. Enablement

### Claims 1, 18, 28 and 32-34

Claims 1, 18, 28 and 32-34 were rejected under the First Paragraph of Section 112 as allegedly lacking enablement, whereas claim 48 and its dependent claims were acknowledged to be enabled. The gist of the Action's premise for rejection is that the Applicants have "not established that the claimed methods would be effective in the treatment of chronic HBV infection." The Action helpfully listed the six factors from *In re Wands* regarding whether the claims are enabled, and then decided that the most important here were the state of the art and the provision of guidance or working examples. The Examiner's assistance here notwithstanding, this basis for rejection cannot be agreed with and is respectfully traversed.

Before showing that the claims are enabled, a possible error in the Action should be corrected. That possible error appears in the first full paragraph of page 11 of the Action where it is asserted that a claimed chimer "protein having into its sequence an immunogenic epitope." That statement is understood to mean that a heterologous sequence having an immunogenic epitope must be present.

It is submitted that the previously amended and present claims include an "insert . . . containing one or more chemically non-reactive heterologous amino acid residues", but that insert is not immunogenic. Indeed, as is discussed at page 42, the inserted "chemically non-reactive heterologous amino acid residues" are added "in Domain II not to function as a B-epitope but to reduce the recognition of the chimeric particle by antibodies circulating in the blood of patients infected with hepatitis B virus."

The Action next notes that the application provides no working examples. While correct, the case law is quite clear that working examples are not needed for enablement. *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982). More importantly, the application contains numerous citations to relevant teachings that illustrate that the HBc molecule is useful in a vaccine for treating chronic hepatitis. See, for instance, the Thoma US Patent No. 6,020,167 that is discussed at page 7 of the specification. A chimer of the present invention is an improvement on a Thoma construct that is claimed and said to work in that patent, and its issuance and presumptive validity, indicate enablement as a matter of law. The case here should be no different.

The Action provides several articles that indicate the usefulness of antiviral small molecule drugs and interferon-α for treating chronic hepatitis, and admits that a vaccine had "limited efficacy", as compared to no efficacy. The Action then asserted that

> none of the identified antigens referred to in art represent the HBc antigens of the presently claimed methods. Thus, the art indicates that the state of the art of therapeutic vaccines against chronic HBV infection is such that there is presently insufficient understanding in the art to indicate what antigens or form of vaccines may eventually be shown useful.

The latter statement cannot be agreed with.

First, the Thoma disclosure has been totally disregarded and that uses HBc itself or T cell-stimulating portions thereof. Similarly, the two previously noted US patents to Thornton et al. also use HBc T cell-stimulating antigens. Still further, the Lebray paper noted in the Action that exhibited "limited efficacy" utilized "a cytotoxic T-cell epitope derived from the HBcAg amino acids 18-27, . . ."

(FLPSDFFPS; Lebray at S156). Further, enclosed as Exhibit B is a copy of press release from PowderMed, Ltd. in England that indicates that a Phase I clinical trial began in March of this year using a DNA vaccine that encodes HBc as part of its immunogen, thus providing a DNA version of a Thoma polypeptide.

It is thus submitted that a review of all of the art indicates that HBc is indeed used and useful as an immunogen for treating chronic HBV infection. It is therefore again submitted that this basis for rejection should be withdrawn.

### Claims 18, 28 and 32-34

Enablement of claims 18, 28 and 32-34 for embodiments wherein Domain I comprises residues 4-75 or 5-75 plus an N-terminal sequence was admitted in the Action. However, claims 18, 28 and 32-34 were rejected as not enabled for embodiments in which the particles include a sequence containing residues 5-75 without an N-terminal sequence. It is believed that this basis for rejection is moot in view of the present amendment to claim 18 in which the N-terminal residue has been amended to be residue 4.

## C. Rejections Under 35 USC §103

### 1) Evidence of Non-Obviousness

Enclosed herewith as Exhibit C is the Declaration of Dr. G. B. Thornton, the President of Apovia, Inc. the former assignee of the subject application and related patents and applications discussed in that Declaration. Dr. Thornton was ultimately in charge of the initial research related to this invention. Dr. Thornton is also the same G.B. Thornton who was the first-named inventor of the Thornton et al., US Patents No. 4,882,145 and No. 4,818,527, noted previously and in the specification.

As will be seen in Paragraph 5A2 of Dr. Thornton's Declaration, immunization using an emulsion provided induced a 4-fold higher number of IFNγ-secreting CD8 T cells as did a similar immunization using the same adjuvant in a non-emulsified aqueous composition.

A similar enhancement of an emulsion over an aqueous preparation is discussed in Paragraphs 5E3 and 5E4 in which results in humans immunized with a HBc chimer malaria vaccine based on ICC-1132 particles are discussed. That particle contains a circumsporozoite (CS) epitope [NANPNVDP(NANP)$_3$] inserted into the immunodominant loop region of the HBc protein between residues 78 and 79 as the one to about 40 amino acid residues containing one or more chemically non-reactive heterologous amino acid residues that render the immunogenic particles less antigenic than the native HBc particles. That particle also includes a *Plasmodium falciparum* T cell epitope [GIEYLNKIQNSLSTEWSPCSVT] bonded to HBc residue position 149.

Dr. Thornton reports that CS-specific IFN-γ-secreting T cells were found in 50% of the vaccinees that received the 50 μg dose of alum-adsorbed vaccine, whereas PBMC of the majority of the human volunteers (6/8) who received a single 20 μg dose of chimer-based vaccine emulsified with Montanide™ ISA 720 showed pronounced proliferation after *in vitro* restimulation with CS protein (6/8).

Dr. Thornton points out in Paragraph 5E6 that the numbers of CS-specific IFN-$\gamma$-positive CD4$^+$ T cells were equivalent to or even greater than those observable after 3 immunizations with a vaccine containing similar CS epitopes based on the hepatitis B surface antigen, rather than the core antigen as is claimed here.

Dr. Thornton discusses the unexpected stability of the particles of claims 61-63 in Paragraphs 7-11. Those particles each had one or both HBc cysteine residues at positions 48 and 107 replaced by another residue, and the HBc cysteine at residue at position 61 present. The data shown in the gel of Paragraph 11 show that the particles of claims 61-63 exhibited greater stability after boiling than did similar particles having the cysteines normally present in the native structure at positions 48 and 107.

### 2) First Rejection , Page et al.

Claims 1, 18, 28 and 32-35 were rejected as allegedly being obvious over the disclosures of Page et al. (Page; WO 01/98333). The gist of this rejection is that although Page does not specifically refer "to the insertion of a non-chemically reactive amino acid residue", Page teaches use of an insert into the HBc immunogenic loop that can be a T cell-stimulating sequence from the Pre S-1 region of HBV that contains one or more non-reactive residues. The epitope defined by Pre S-1 sequence position numbers 21-28 was noted from page 15 of Page, whereas approximately 50-residue long Pre S-1 epitope insertions from positions 31-80 are shown inserted at or near the HBc C-terminus in Table 2 at page 25 of the application. Those epitopes were said to contain chemically non-reactive residues, and thus the modification of the HBc sequence recited in the claims would be deemed obvious. This basis for rejection cannot be agreed with and is respectfully traversed.

It is first noted that the Second Election that is acknowledged in the Action elected Claim Group II and accompanied an amendment to the claims in which claims drawn to "methods of treating chronic hepatitis using a recombinant HBc comprising a heterologous immunogenic epitope" were cancelled or such recitations were otherwise amended out of the claimed subject matter. The Pre S-1 epitopes that are being relied-on here from the Page disclosure are the very immunogenic epitopes whose subject matter was removed from the claims. It is therefore believed that this rejection is inapt as the election removed the subject matter said to be made obvious.

Additional evidence for the removal of the claimed subject matter from that suggested by Page is the fact that claims 2-17 have been cancelled. Those claims included dependent claim 12, below, that recited that an insert to the immunogenic loop contained "a heterologous linker residue for a conjugated epitope".

> 12. The method according to claim 1 wherein said chimer contains a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop.

It is thus submitted that an inserted sequence cannot have a reactive residue because the presence of that residue would convert the sequence into a sequence containing "a heterologous linker residue" that is not claimed. Thus, the Pre S-1 21-28 sequence noted at page 12 of Page contains an aspartic acid and a histidine residue both of which are chemically reactive, and one of which is used as part of a linker sequence as noted in the paragraph bridging pages 60-61 of the present specification. It is thus submitted that this rejection should be withdrawn.

It is further submitted that the present amendments to the claims to recite that the sequence insert renders "the immunogenic particles less antigenic than the native HBc particles" further removes the subject matter here claimed from that disclosed by Page. Page disclosed enhancing the immunogenicity of the particles by the addition of an immunogenic sequence. Here, the chimers contain a sequence inserted into the loop whose purpose and effect is to diminish the immunogenicity of the loop region sequence. Again, the rejection should be withdrawn.

### 3) Second Rejection, Page in view of Johnson

Claims 48-51 have been rejected as allegedly obvious from the disclosures of Page as above, also including its teaching that an adjuvant can be used with the chimer, further in view of the teachings of Johnson et al. US Patent No. 6,303,347 (Johnson). The Page teaching is used as it was in the preceding rejection, whereas the Johnson teaching of the use of so-called AGP adjuvants. The AGP group of adjuvants is taught to be useful in cell-mediated as well as antibody immune responses. The Action concludes that it would therefore have been obvious to include an AGP adjuvant in a composition directed to the induction of anti-HBV T cell responses even though the Action admits that Johnson does not teach or suggest the use of TLR-4 or TLR-9 agonists as is claimed. This basis for rejection is respectfully traversed.

It is respectfully submitted that the combined teachings neither teach nor suggest the subject matter claimed in claims 48-51, nor that in claims 58, 59, 60 or 63. More specifically, as noted before, Page teaches nothing about adding one or more residues to the loop to lessen antigenicity toward anything, much less the native HBc particles. That lessening of antigenicity is also not coupled with use of the particles in an emulsion, nor is it taught or suggested that such a use would provide an enhanced T cell response after immunization as is shown in Dr. Thornton's Declaration. Still further, neither teaching suggests the use of the unexpectedly stable particles of claim 63 in combination with the other recited claim elements. It is submitted that this rejection should be withdrawn.

### 4) Third Rejection, Thoma in view of Birkett and Pumpens

Claims 1, 18, 28 and 32-34 were rejected as allegedly obvious from the combined teachings of Thoma (WO 92/11368; US No. 6,020,167) in view of Birkett et al. (US No. 6,942,866) and Pumpens et al. *Intervirol*. 38:63-74. The Action combines the teachings of Thoma for treating a chronic hepatitis B infection using a carrier protein that preferably formed a particle fused to a HBc T cell epitope. The constructs recited in Thoma preferably used HBc or HBs was as a carrier, although several other sequences were recited. (See, column 4, lines 5-13.) Both the T cell peptide and the carrier were said to preferably be myristylated. (See, columns 3 and 4 at lines 62 and 20-21, respectively.) The Action asserts that Thoma teaches that a desired sequence can be "inserted into any of the C-, the N-or internally to the carrier particle". The Birkett patent is directed to a malaria vaccine that uses a C-terminal truncated HBc sequence along with a 20-mer malarial peptide insert into the HBc loop to provide an immunogen against malaria. The Pumpens teaching is used to provide the place into which the sequence is inserted, the loop, and C-terminal truncation. The Action also admits that the Thoma patent does not teach either truncation of the C-terminus of the HBc molecule nor that the truncated molecule should have 1-3 cysteines within 30 residues of the C-terminus. This basis for rejection cannot be agreed with and is respectfully traversed.

It is submitted that the art has again been scoured for teachings, which when individually culled and summed, seem to add up to the claimed subject matter, but that are actually taken out of their own context in carrying out that summation. Thus, Birkett teaches use of a HBc chimer that contains malarial B and T cell epitopes that would not be thought of by a worker of ordinary skill as being useful for hepatitis. Thoma's PreS-1 sequence is not a sequence "that render[s] the immunogenic particles less antigenic than the native HBc particles". It is rather an immunogenic sequence whose presence makes the chimer

MORE immunogenic than the native particle. Specific locations for insertion within the HBc sequence were never provided by Thoma, thereby failing the modern description requirement. The Pumpens teachings are relied on for teaching where an immunogenic epitope should be added in a chimer, but are silent on where one should place an inserted sequence that makes "the immunogenic particles less antigenic than the native HBc particles".

Thus, picking and choosing only so much as is useful and disregarding the context, the bones of the claimed subject matter can be assembled to approach the skeleton of the claims, but there is muscle or sinew on those bones, nor a rationale laid out in the forward teaching art for assembling the bones as they have been in the Action, aside from that disclosed in this application. For example, there is no reason to use one to three stabilizing Cys residues "within about 30 residues from the C-terminus of the chimer molecule" because Pumpens teaches at page 67, left column, that adding residues into the sequence "exert a stabilizing effect on chimeric HBcΔ derivatives…" Further, if one were to take the preferred HBc particle-forming sequence, where is the similarly preferred myristylation that Thome recites. Further, where is the HBs sequence that Thome used for his actual results. The Birkett teachings of an anti-malaria vaccine that has separate malarial B and T cell epitopes in an HBc chimer teaches a skilled worker nothing about treating hepatitis or "one or more of gamma-producing CD 8+, CD 4+ T cells and cytotoxic T lymphocytes against hepatitis B virus".

It is thus submitted that if one were to consider ALL of the of the teachings of the art relied-on here as the Court has admonished [*In re Kuderna and Philllips*, 165 USPQ 575, 578-579 (CCPA 1970)], and not just those selected out to sound like the invention, this rejection would be withdrawn. Put somewhat differently, as noted in *In re Shaffer*, 108 USPQ 326, 329 (CCPA 1956), "[t]he art applied should be viewed by itself to see if it fairly disclosed doing what an applicant has done. If the art did not do so, the references may have been improperly combined." It is believed that the teachings of the relied on art does not fairly disclose the claimed invention and it is thus respectfully requested that this rejection be withdrawn.

### 5) Fourth Rejection, Thoma in view of Birkett, Pumpens and Johnson

Claims 48-51 have been rejected as allegedly obvious in view of the combined teachings of Thoma in view of Birkett, Pumpens and Johnson as each has been discussed previously. In view of the deficiencies in each of the combinations and individual teachings already discussed, this basis for rejection cannot be agreed with and is respectfully traversed.

The deficiencies of the combined teachings of Thoma, Birkett and Pumpens as applied here that are discussed immediately above are incorporated here by reference. It is submitted that just as Section 112, First Paragraph, requires that the applicant must mark a trail through the woods by supplying blaze marks on trees [*In re Ruschig*, 154 USPQ 118, 122 (CCPA 1967)], the art asserted in an obviousness rejection must also contain blaze marks for the skilled worker to find his/her way through the forest to the tree of the claims. The added teachings provided by the Johnson disclosures are, however, insufficient to add the required blaze marks sufficient to provide a path through the woods to the claims. More recently, *In re Fine*, 5 USPQ2d 1596, 1598 (Fed Cir 1988), similarly held that the Patent Office can satisfy its burden in establishing a *prime facie* case of obviousness "by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." [Citations omitted.] That burden has not been met.

It is further respectfully submitted that the combined teachings neither teach nor suggest the subject matter claimed in claims 48-51, nor that in claims 58, 59, 60 or 63, for the same reasons that have already been discussed.

More specifically, the combined teachings provide no disclosure about adding one or more residues to the loop to lessen antigenicity toward anything, much less the native HBc particles, but rather seek to enhance immunogenicity. That claimed lessening of antigenicity is also not coupled with use of the particles in an emulsion, nor is it taught or suggested that such a use would provide an enhanced T cell response after immunization as is shown in Dr. Thornton's Declaration. No combination of those teachings suggests the use of the unexpectedly stable particles of claim 63 in combination with the other recited claim elements. It is submitted that this rejection should be withdrawn.

### D. Further Art

An International Search Report from the PCT carried out by the present Examiner has been received, after being mailed on 17 July 2006. It is therefore apparent that that art has not been in the possession of a person associated with this application for more than three months. A copy of that Report and the non-redundant art it listed are enclosed. Also enclosed and listed on the form PTO/SB/08B are copies of the art noted in Dr. Thornton's Declaration.

## E. Summary

Claims 1, 18 and 48 have been amended, and claims 54-63 have been added. Each basis for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

Large entity status is now believed to apply to this application.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition. This paper is being filed in duplicate.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By

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Enclosure
- Petition and Fee
- Exhibits A-C
- Form PTO/SB/08B

## CERTIFICATE OF MAILING

I hereby certify that this Reply and Amendment, in duplicate, and the Petition and fee, and the stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on September 15, 2006.

Edward P. Gamson